Original Article

Randomized clinical trial comparing clinically relevant sedation outcome measures in healthy dogs after intramuscular administration of medetomidine in combination with midazolam or butorphanol for routine imaging procedures.

D. Le Chevallier. *, L.Slingsby J.C Murrell.

[a]*Bristol Veterinary School,University of Bristol, Langford. Bristol BS40 5DU,UK*

* Corresponding author. Tel.: +447958361824.
E-mail address: dl8832@bristol.ac.uk

Abstract

The objective of the study was to investigate the sedative effects of medetomidine in combination with midazolam or butorphanol for routine imaging procedures. Eighty client owned dogs were recruited for the prospective, randomised, blinded clinical study. Dogs were randomly assigned to receive one of four treatments IM at time T0: 30 μg/kg medetomidine (med30), 20 μg/kg medetomidine combined with 0.3 mg/kg butorphanol (med20but0.3), 20 μg/kg medetomidine combined with 0.3 mg/kg midazolam (med20mid0.3) and 10 μg/kg medetomidine combined with 0.3 mg/kg midazolam (med10mid0.3). The level of sedation was evaluated using a composite sedation scale assessed by one investigator (0=no sedation, 15=profound sedation). The number of dogs that were deemed adequately clinically sedated and the dose of propofol administered as rescue sedation were recorded. Data are presented as mean ± standard deviation (SD).

Mean sedation scores at T30 in the groups that received med20but0.3 (9.8 ± 4) and med20mid0.3 (8.9 ± 4.4) were not statistically significantly different from each other but were significantly different to med10mid0.3 (5.6 ± 3.6). Only med20but0.3 was significantly associated with adequate clinical sedation while med10mid0.3 was associated with 85% sedation failure rate. The rescue sedation dose of propofol for the med10mid0.3 group (1.5 ± 1 mg/kg) was significantly higher than the other treatments. A sedation score ≥10/15 was a satisfactory cut off to predict adequate clinical sedation.

In healthy dogs, the combination of medetomidine with midazolam did not provide comparable sedation to the same dose of medetomidine in combination with butorphanol in a clinical setting.

Keywords: Sedation; Dog; Midazolam; Medetomidine; Butorphanol; Imaging

Introduction

Sedation of small animals is a daily occurrence in veterinary practice. To perform procedures such as imaging, deep sedation, defined as patients being immobile and unresponsive to external stimuli, is usually required (Koroglu et al., 2005; Murrell, 2016). In healthy companion animals, alpha-2 adrenoreceptor agonists, such as medetomidine are the most commonly used sedatives in the UK (Brodbelt et al., 2008). Medetomidine provides reliable and profound sedation which can be rapidly reversed with atipamezole (Pypendop and Verstegen, 1998; Murrell, 2016). However, alpha-2 adrenoreceptor agonists also have severe cardiovascular consequences such as peripheral vasoconstriction, marked bradycardia and decreased cardiac output (Kojima et al., 2002; Murrell and Hellebrekers, 2005). Medetomidine can be effectively combined with opioid agents such as butorphanol to provide the same level of sedation while requiring lower doses of alpha-2 adrenoreceptor agonists. In dogs, the combination of medetomidine with butorphanol is widely reported in the literature and this combination is licensed for canine sedation in the UK. Compared to medetomidine alone, the addition of butorphanol provides a quicker onset, and more profound sedation whilst using lower doses of medetomidine (Muir et al., 1999; Girard et al., 2010).

Benzodiazepines may also be a potential alternative agent for combination with medetomidine in place of opioids. Midazolam is well absorbed intramuscularly and has minimal cardiovascular effects (Schwartz et al., 2013; Hopkins et al., 2014). While in human medicine, midazolam is the most commonly used sedative[a] and is effective (Godwin et al., 2014), in veterinary medicine it is rarely used alone or in combination in healthy dogs. When administered as a single agent it provides minimal or no sedation in healthy dogs (Court and Greenblatt, 1992). However, a few experimental studies have suggested that when midazolam when combined with medetomidine, sedation was much improved compared to medetomidine alone (Hayashi et al., 1994; Kojima et al., 1999). Additionally, Hayashi et al.

(1994) reported the combination to be comparable or even superior with better muscle relaxation to the combination of medetomidine with butorphanol in dogs (Hayashi et al., 1994; Kojima et al., 1999).

The present study evaluated the effect of medetomidine in combination with butorphanol compared with midazolam by using a sedation scoring system, recording the number of dogs reaching clinical sedation, the rate of sedation failures and the dose requirement for rescue sedation with propofol. It was hypothesized that the sedative effect of medetomidine in combination with midazolam would be similar to the sedative effect of medetomidine and butorphanol.

Materials and methods

Animals

The study protocol was approved by the Bristol University Animal Ethical Review Committee on the 24th of September 2015 (VIN/15/003) and informed owner consent was obtained for all dogs that were enrolled on the study. The study was also conducted under an Animal Test Certificate (42273/002) and complied with Good Clinical Practice standards. Eighty client-owned dogs scheduled for elective diagnostic imaging procedures at a University hospital were recruited. All animals were healthy based on full clinical examination and were classified as American Society of Anesthesiologists (ASA) I or II, had no or mild pain at presentation and weighed between 10 and 40 kg. One investigator collected all the data and was unaware of treatment allocation.

Study design and treatments

The dogs were randomly assigned to receive one of the four sedation treatments. Randomisation was performed by block by a random number generator using Excel

Microsoft Formulas (Microsoft Software 2014) depending on body weight (10-25kg SSMALL and 26-40kg SLARGE) in the four treatment groups: the positive control: 20 μg/kg medetomidine with 0.3 mg/kg butorphanol (med20but0.3), the negative control : 30 μg/kg medetomidine (med30), 20 μg/kg medetomidine with 0.3 mg/kg midazolam (med20mid0.3) and 10 μg/kg medetomidine with 0.3 mg/kg midazolam (med10mid0.3).

The treatment administrator was a registered nurse or veterinary surgeon. The allocation sheet was enclosed in an opaque sealed envelope. The veterinary surgeon involved in the randomization process and the treatment administrators were not involved in the data collection. All drugs, medetomidine (1 mg/mL, Sedastart, Animal Care Limited), butorphanol (10 mg/mL, Alvegesic, Dechra Veterinary Products), midazolam (5 mg/mL, Dormazelam, Regivet BV) and atipamezole (5 mg/mL, Sedastop, Animal Care Limited) were administered into the lumbar muscles using a 25mm long needle and an appropriate sized syringe for the set volume. When two drugs were used for sedation they were injected separately into the left and right lumbar muscles because there are no data on the compatibility of these drugs when mixed in the same syringe.

Experimental protocol

Once recruited, the dogs were taken in the recovery room. This is the designated area for animals to be recovered from anaesthesia and is a quieter area compared with the main dog wards. A baseline heart rate (HR), respiratory rate (RR), body temperature (BT), sedation score and body condition score (BCS) and pain score using a simple descriptive scale were collected (Appendix: Supplementary table 2). An intravenous catheter was placed in the cephalic vein prior to sedative administration. The time of sedative drug administration was Time = 0 (T0).

Assessment of sedation

Sedation was scored using a composite descriptive scale described by Raszplewicz et al. (2003) and Gurney et al. (2009) (Appendix: Supplementary table 1) (Raszplewicz et al., 2013).

Sedation was scored during the initial clinical examination of the dog. Following the test drug administration (T=0), sedation was scored every 5 min until T20, then every 10 min until atipamezole administration (at T60 min). The time of peak sedation was considered to occur at T30.

Rescue sedation and treatment failure

Adequacy of sedation was assessed by the investigator. Sedation was deemed inadequate if the dog did not assume spontaneous lateral recumbency within 40 minutes of the test drug administration and was still responsive to stimulation (such as moving the dog to the trolley to be moved to imaging) at this time point. The data from these dogs were recorded as a treatment failure. If the dog was sufficiently sedated to be moved to imaging, but then not sufficiently sedated to allow imaging, propofol was administered IV to effect in 1 mg/kg aliquots and the dose recorded. If a dog required rescue propofol during imaging it was also counted as a treatment failure.

Time to imaging

The time that imaging started and finished was recorded. It was assumed that time to imaging was the time it took to achieve adequate sedation for imaging from drug administration.

Monitoring of physiological variables

During the procedure, HR and RR were measured manually by palpating the femoral pulse and by visually observing respiration over a 15-s period. This was done immediately before the sedation score was measured to avoid an artificial increase in HR and RR caused by the manipulation of the patient for the sedation score.

Monitoring of adverse events

Any adverse events that occurred during the study were recorded.

Statistical analysis

A power calculation to determine sample size was based on a study by Kuusela et al. (2000) using the same composite sedation scoring system (Kuusela et al., 2000). They indicated that 17 dogs per group were needed for a statistical power of 90% to detect a difference in sedation scores of 25% with an alpha error of 0.05. Therefore, it was decided to recruit 20 dogs/ group in the present investigation.

Data were assessed for normality and homocedasticity of variance using Shapiro-Wilk test and distribution. A one way between groups analysis of variance (ANOVA) was used to compare sedation score at T30, rescue sedation dose and time to imaging. A mixed between-within ANOVA was used to compare sedation scores, HR, RR and BT over time. Wilks' lambda was used to assess interaction between factors and Partial Eta Squared to examine its effect size.

A Chi-square test was used to compare the number of dogs per treatment group that were clinically sedated, were treatment failures and adverse event incidence. When post-hoc testing was carried out, the *P* value at 0.05 was adjusted by Bonferroni correction *P*/*n*

(Beasley and Schumacker, 1995). Non-parametric data (age, body condition score: BCS, pain level of the dog before sedation) were assessed using Kruskal Wallis analysis of variance. *P* values < 0.05 were considered statistically significant apart from when a Bonferroni correction was applied. Data were analysed using SPSS 18 (IBM, NY,USA).

Ancillary analyses were performed to determine a clinically relevant cut off score for the sedation scoring system used in this study. The aim was to find a reliable cut off score that was sensitive enough to identify the proportion of dogs that were clinically sedated from the ones that were not. To determine the sensitivity and specificity and the appropriate cut-off score of the sedation scoring system, receiver operating characteristic curve (ROC) and two-by-two tables to determine the sensitivity, specificity positive predictive value and negative predictive value were performed (Hanley and Mcneil, 1982; Abdul Ghaaliq Lalkhen, 2008).

Normally distributed data are presented as mean ± standard deviation (SD).

Results

Demographic data from the four groups are shown in table 1. There were no significant differences in age, body weight, sex distribution, BCS and pain scores between the treatment groups. There was no association between treatment groups and imaging procedures, either radiography or computed tomography (X^2, p=0.37). The imaging comprised 41 radiographic procedures and 39 CT procedures. There were no significant differences in the duration of imaging between the treatment groups with a mean time of (24 ± 15) min (P=0.18).

Of the eighty dogs recruited to the study all the dogs were included in analysis of sedation scores over time, sedation scores at T30, sedation failure rate and rescue sedation dose of propofol. The sedation scores over the first 30 min changed significantly with time, increasing after treatment administration in all the groups (P<0.005). There was not a statistical difference between the treatment groups in terms of sedation score over the first 30 min of data collection (P=0.94) (figure 1). At T30 there was a significant difference in sedation score between the treatment groups (P=0.006). Numerically the sedation scores in the med20mid0.3 (8.9 ± 4.4) and med20but0.3 (9.8 ± 4) groups were greater than the med30 (7.5 ± 2.7), however med30 was not statistically significant from med20but0.3 or med20mid0.3. Med10mid0.3 (5.6 ± 3.6) had the lowest sedation score and was significantly different from med30, med20but0.3 and med20mid0.3 (figure 2) (table 2).

In this study, 46 (57.5%) of all dogs were considered as sedation failures. There was a significant association between treatment group and failure rate (P=0.001). Dogs in the Med20but0.3 group were significantly less likely to be a treatment failure and accounted for only 22% of the treatment failures, while dogs in the med10mid0.3 group were significantly more likely to be treatment failures with 85% of cases being sedation failures (see table 2).

The amount of rescue sedation (propofol dose) did significantly differ between the treatment groups (P=0.001). Med30 (0.9 ± 0.6 mg/kg propofol) was not statistically significantly different from the other treatments. Med20but0.3 (0.4 ± 0.7 mg/kg) and med20mid0.3 (0.7 ± 0.9 mg/kg) were not statistically different from each other but were statistically significantly different to med10mid0.3 (1.5 ± 1 mg/kg), with a higher dose of propofol required in the med10mid0.3 group (table 2).

Physiological variables

Heart rate, RR, and BT remained within a normal clinical range in all dogs during the study. Heart rate and RR decreased significantly over time (P<0.005). There was not a statistically significant difference between treatments for the physiological variables HR (P=0.4), RR (P=0.26) and BT (P=0.6). The med10mid0.3 group had a trend for having less marked effects on the HR and RR over time.

Sedation scoring assessment

Based on clinical judgement two cut off scores, 10/15 and 11/15, were analysed. When all dogs were considered together the range of sedation scores at T30 was to 1-14 with a mean score of 7.95 ± 4. The cut off sedation score of 11/15 resulted in high sensitivity 98 % (dogs identified as being appropriately clinically sedated). The specificity (dogs identified as not being suitability sedated) was suboptimal at 65% with AUC of the ROC of 0.8. The area under the ROC curve characterises the general accuracy of a test. When the value approaches one it shows a high sensitivity and specificity (Abdul Ghaaliq Lalkhen, 2008). A 10/15 sedation score cut-off was more appropriate with a slightly lower sensitivity of 95.5% and improved specificity of 85% with a higher AUC of the ROC of 0.9. An AUC of >0.9 is classed as an excellent test (table 3).

Adverse events

Seventeen dogs experienced an adverse event during the study (table 4). There was no significant association between the treatment groups and adverse events (p=0.06).

Discussion

The aim of this study was to evaluate whether the intramuscular combination of medetomidine and midazolam provided similar sedation to a standard butorphanol and medetomidine combination in a clinical setting for sedation for imaging procedures. Once all the measured variables were assessed together, the combination of medetomidine and midazolam, at the doses investigated, did not provide consistent evidence that it was a reliable and adequate sedative.

At T30, there was no difference in sedation scores between med20but0.3 and med20mid0.3. However, in our study, adequate clinical sedation was only achieved and associated with the combination of med20but0.3. An explanation for the discrepancy between sedation score and clinical sedation in the present study may be that the criteria used in the sedation scoring system may not uniquely measure sedation, resulting in high sedation scores for med20mid0.3 compared to med20but0.3 although the plane of sedation was actually different. Midazolam alone causes rapid and profound muscle relaxation (Adams et al., 1985; Court and Greenblatt, 1992). By comparison, medetomidine causes dose-dependent sedation associated with loss of posture and reduced consciousness (Kuusela et al., 2000) Although the sedation scoring system used in the present study was created to evaluate alpha-2 adrenoreceptor agonists sedation, it may not be adequate when assessing a combination of midazolam with the alpha-2 adrenoreceptor agonist. The muscle relaxation may have not only impacted posture scoring but also other dynamic behavioural endpoints such as resistance to lateral recumbency, response to noise and general appearance.

At T30, sedation scores in the med10mid0.3 group were significantly lower than the other treatments suggesting that this combination achieved only mild sedation. It has been reported that dogs administered medetomidine at 10 µg/kg intramuscularly are still alert and responsive (Hammond et England, 1994). The addition of midazolam did not seem to provide further deepening of sedation in the study. Our observations are supported by Canfrán et al. (2016). Using the same sedation scoring system as the one used in the present study they reported a median score of 8 with 5 µg/kg dexmedetomidine and 0.3 mg/kg midazolam which was not significantly different from dexmedetomidine alone. Compared to the experimental Canfrán et al. (2016) study, our sedation score was much lower with med20mid0.3. The difference may be caused by the 'controlled environment' of the Canfrán et al. (2016) study as veterinary hospitals are stressful environments for dogs and anxious dogs are less likely to sedate (Riviere et Papich, 2009; Canfrán et al., 2016;).

Initially the positive control for the study was 10 µg/kg of medetomidine and 0.1 mg/kg of butorphanol and medetomidine 30 µg/kg was the negative control. However, due to the high sedation failure rate in the initial phase of the study of the positive control the doses of both drugs were increased. A high failure rate meant that the investigator was frequently assessing dogs for 40 min, which was delaying the routine of the hospital. The difference in medetomidine dose between the treatment groups and the negative control is a limitation of the study as it makes comparisons between treatment groups challenging. Furthermore, the higher dose of butorphanol was out of the summary of product characteristics (SPC) 'sedative dose range' and was in the 'analgesic dose range'. Therefore, some of the additional sedative effects of the positive control may have been related to better analgesia especially during positioning of the dog for imaging. The population of dogs in the study were recruited from the orthopaedic department with an over representation of middle-aged dogs. The pain level was assessed before recruitment and only non-painful or mildly painful dogs were included in

the study. However, all of the dogs in the study were suffering from or had suffered to some degree with an orthopaedic issue. As such, manipulation of the limbs may have been more painful than in 'normal' dogs. Invasiveness of the imaging procedure was not scored, although the diagnostic imaging procedures were balanced between the treatment groups. If a lower dose of butorphanol had been used, as was originally proposed, it is possible that the positive control might not have been associated with sedation success compared to the midazolam combinations.

Using sedation scores as a primary outcome measure is challenging especially in a clinical setting where it is difficult to control multiple variables. This study has revealed the importance of incorporating into the design, the outcome of the sedation and failure rates, when assessed in a clinical setting. This will provide more reliable and clinically convincing results of the potency of sedatives in future studies.

Conclusion

This study highlights the importance of assessing adequacy of sedation for a procedure as an outcome measure especially in a clinical environment. This is particularly relevant when transferring results to clinical practice. Our initial hypothesis that medetomidine-midazolam would provide adequate sedation comparable to medetomidine-butorphanol was not supported. Although the study suggests similar planes of sedation, medetomidine-midazolam was not an adequate combination for sedation for routine procedures requiring profound sedation. Furthermore, the study also demonstrated that lower doses of medetomidine with midazolam provided poor sedation associated with a high failure rate and a high dose requirement for rescue sedation medication.

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Conflict of interest statement

Regivet supplied the midazolam used in this study. However, they played no role in the study design nor in the collection, analysis and interpretation of data. None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

Appendix

Supplementary data associated with this article can be found, in the online version, at doi: ...'

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323

Table 1

Characteristics of dogs for all treatment groups.

Treatments	Age (years, months)	Weight (kg)	Body condition score (/9)	M:MN:F:FN	Pain scores	total
Med30	5 [10]	25.6 ± 7.6	5.5 [4]	2:5:6:7	0 [1]	20
Med20but0.3	3.9 [7.6]	24.4 ± 8	5 [4]	2:5:4:7	0 [1]	18
Med20mid0.3	4 [7.3]	24.3 ± 7	5 [5]	4:6:6:6	0 [1]	22
Med10mid0.3	3.5 [7.3]	25 ± 7.7	5.5 [5]	3:6:8:3	0 [1]	20
All dogs	4 [10.6]	24.8 ± 7.7	5 [6]	24:23:11:22	0 [1]	80

Data are presented as mean ± (standard deviation) SD or median [range], age in years and months, body weight in kg, body condition score (/9), sex distribution with number of dogs. M:MN:F:FN : Male:MaleNeutered:Female:FemaleNeutered, pain as a score (0-3 ; 0 no pain, 3 severe pain) n=80.

Table 2

Sedation scores at T30 (30 min after administration of the test drug(s)), propofol dose required for rescue sedation and rate of sedation failure for dogs treated with 30 μg/kg medetomidine (med30), 20 μg/kg medetomidine with 0.3 mg/kg butorphanol (med20but0.3), 20 μg/kg medetomidine with 0.3 mg/kg midazolam (med20mid0.3) and 10 μg/kg medetomidine with 0.3 mg/kg midazolam (med10mid0.3).

	Sedation score at T30	Rescue sedation dose of propofol	Sedation failure rate
Med30	7.5 ± 2.7[#]	0.9 ± 0.6	80%
Med20but0.3	9.8 ± 4[#]	0.4 ± 0.7	22%*
Med20mid0.3	8.9 ± 4.4[#]	0.7 ± 0.9	54%
Med10mid0.3	5.6 ± 3.6	1.5 ± 1	85%*

Data are presented as Mean ± standard deviation (SD) or % . [#] values differ significantly (P<0.05) from med10mid0.3, * statistically significantly different from each other at P<0.05, n=80.

Table 3.

Sensitivity and specificity of the sedation scoring system for assessing clinical sedation .

Sedation score cut-off (/15)	≤10	≤11
Sensitivity	95.5%	98%
Specificity	85%	65%
Positive predictive value	90%	79%
Negative predictive value	93.5%	95.5%
AUC, 95% CI	0.9, 0.8-1	0.8, 0.7-0.9

AUC, area under the curve; CI, confidence interval

Table 4

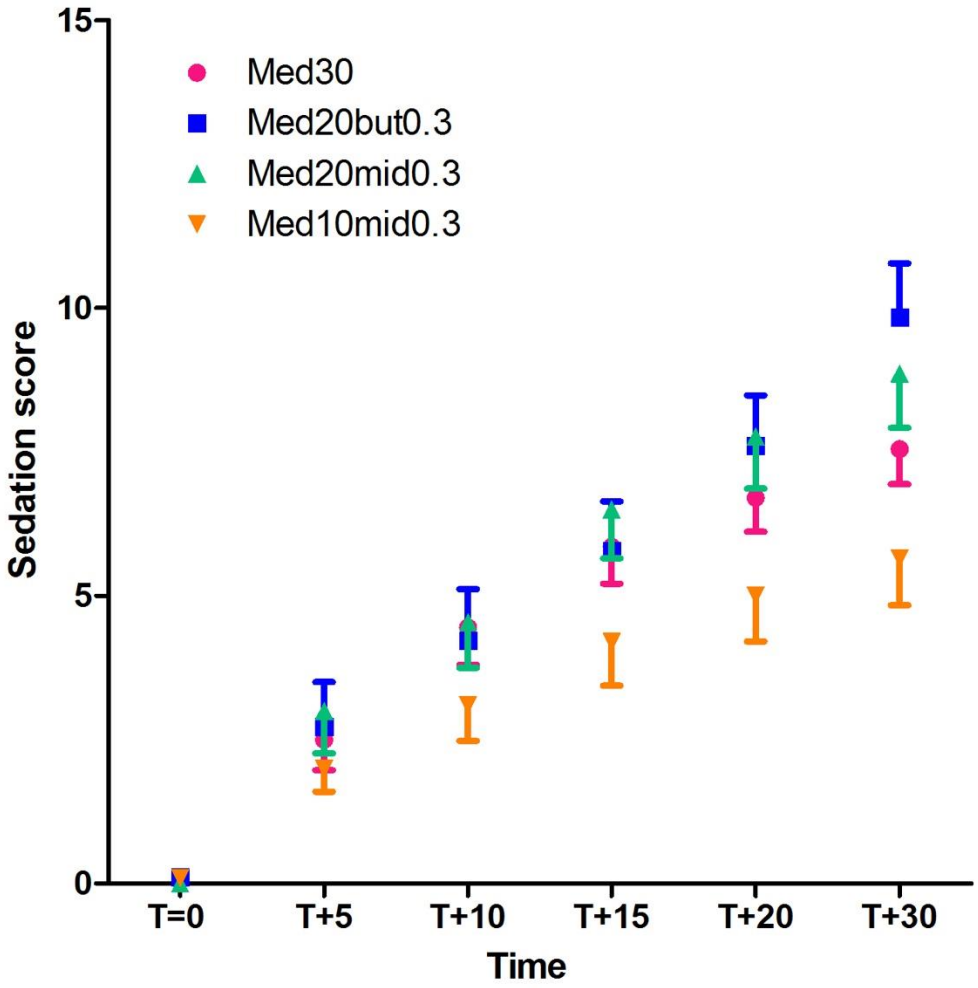
Adverse events for all treatment groups..

	Vomiting	Prolonged recovery	Myoclonic episode	Paradoxical behaviour
Med30	2	0	0	1
Med20but0.3	0	2	0	0
Med20mid0.3	3	0	0	2
Med10mid0.3	1	0	1	5
All dogs	6	2	1	8

Data presented as number of dogs, n=80. Paradoxical behaviours :Defined as agitation,excitation, vocalisation and sound hypersensitivity. Myoclonic episode: Following propofol administration

Figure 1.

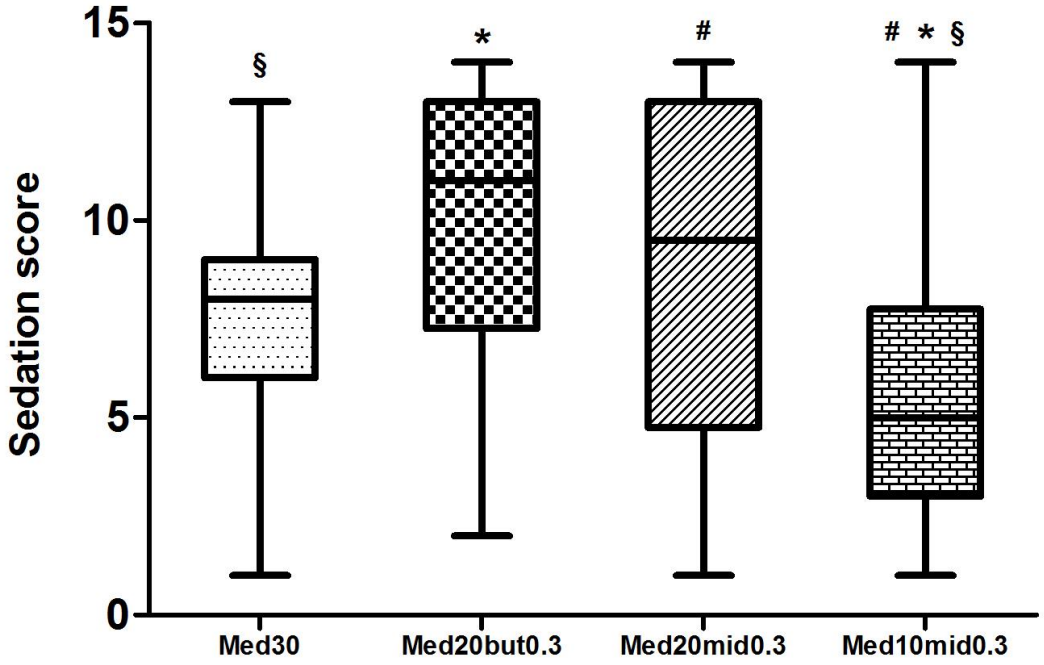
Sedation scores over time for all treatments.



Data are presented as mean ± SE and time in min, n=80

Figure 2.

Sedation scores at T30 for all treatments**.**



Data presented as box and whisker plots *values differ significantly (P<0.05) between med10mid0.3 and med30; # values differ significantly (P<0.05) between med10mid0.3 and med20but0.3 and med20mid0.3; § values differ significantly (P<0.05) between med30 and med10mid0.3, n=80.

Appendix:

Supplementary table 1

Composite simple descriptive sedation score described by Raszplewicz et al. (2003) and Gurney et al. (2009).

Criteria	Descriptor	Score
Spontaneous posture	Standing	0
	Sternally recumbent	1
	Laterally recumbent	2
Palpebral reflex	Brisk	0
	Slow	1
	Absent	2
Eye position	Forward	0
	Rotated ventrally	2
Respond to sound (handclap)	Body movement	0
	Head movement	1
	Ear twitch	2
	No reaction	3
Resistance to lateral recumbency	Full (stands)	0
	Moderate restraint required	1
	Mild restraint required	2
	No resistance	3
Overall appearance	No sedation apparent	0
	Mild sedation	1
	Moderate sedation	2
	Well sedated	3
Total possible sedation score		15

Supplementary table 2

Simple descriptive scale (SDS) used to grade pain level

Descriptor	Score
No pain	0
Mild pain	1
Moderate pain	2
Severe pain	3